

Neurological and psychiatric side effects of cimetidine—report of 3 cases with review of the literature

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Summary

Neurological and psychiatric side effects of cimetidine are reviewed in 47 cases from the literature, and 3 further cases are described. Confusion, psychomotor restlessness, hallucinations and disorientation, stupor and coma were the main features; some had convulsions and a few exhibited focal neurological deficits or neuropathies. The signs appeared within 2 days in almost half of the patients, and remitted in most within 2-3 days. Predisposing factors, of which more than one may be present, are advanced age, hepatic or renal dysfunction, or severe underlying disease. The 3 cases described were all old, one had cirrhosis with bleeding oesophageal varices, and one had renal failure with nephrotic syndrome and amyloidosis.

In view of the increasingly wide use of cimetidine, conditions in which there is decreased metabolic breakdown, or excretion, or predisposition to increased brain levels should prompt careful follow-up, and possibly a lower dosage regimen, especially in elderly patients.

Introduction

Cimetidine, the histamine H₂ receptor blocking agent, is widely used for the treatment of duodenal ulcer, and is also administered in peptic oesophagitis, hypersecretory disorders and in acute gastrointestinal bleeding. The drug is generally well tolerated in doses of 1000-1200 mg daily. However, many side effects have been described. The first case of cimetidine-induced mental confusion was reported by Grinson in 1977, but since then mental confusion, psychiatric disorders and neurological abnormalities have been occasionally reported. Predisposing factors for these side effects are claimed to be old age and renal and hepatic failure. Coma in an old person suffering from metabolic failure, and who is receiving cimetidine

may thus pose a difficult diagnostic problem. Withdrawal of cimetidine can indicate the probable cause of the clinical deterioration. In this paper 3 elderly patients are described who presented with coma or confusion following the administration of cimetidine. In 2 of them, there was concurrent renal or hepatic failure but the mental state returned to normal on cessation of the drug. Forty-seven patients with neurological and psychiatric disorders due to cimetidine who were reported in the literature from 1977 are reviewed and analysed regarding associations of age and clinical status.

Case reports

Case 1

An 80-year-old woman underwent nail-plate insertion for hip fracture. In the postoperative period she developed pulmonary emboli, and was treated with heparin. At this time renal and liver function tests were in the normal range. Three days later the patient developed mottled oesophagitis. Cimetidine tablets 200 mg 3 times daily were started. One day later the patient became drowsy and confused. No additional pathology was found. Cimetidine was discontinued and 24 hr later she became fully orientated.

Case 2

An 82-year-old woman was admitted with haematemesis and melaena. Apart from mild oedema of the legs physical examination was normal, but the haemoglobin was 9.3 g/dl, blood urea nitrogen (BUN) 27 mmol/litre and serum creatinine 415 µmol/litre. Serum albumin was 23 g/litre, but other tests of liver function and serum electrolytes were normal. Endoscopy and biopsy showed acute and chronic oesophagitis and upper gastro-intestinal X-

rays were normal. Cimetidine 1 g daily i.e. (200 mg three times daily and 400 mg at night) was given, but this and other conservative measures failed to stop the bleeding, and on the 3rd day laparotomy was performed. The findings at operation were cirrhosis and oesophageal varices and a feeding gastrostomy was performed. Postoperatively she continued to have cimetidine 1 g daily as well as metoclopramide 10 mg 3 times daily. Pitressin was given for 48 hr. On the 7th postoperative day, she became stuporous, and within hours sank into hyporeflexic coma, reacting only to painful stimuli. There was no asterixis. All drugs were stopped, and the patient received i.v. glucose 20%, neomycin 4 g by mouth and 200 mg spironolactone for 24 hr. Within 24 hr the patient became responsive to commands, and 3 days later she was wide awake eating orally. Electroencephalogram (EEG) performed while she was comatose showed slow wave patterns with bursts of fast wave activity, consistent with drug-induced toxic encephalopathy. There were no triphasic waves. A repeat EEG after her return to consciousness showed that the fast wave periodic pattern had disappeared.

Comment. The onset of coma within a few hours, the lack of tremor, the preservation of normal liver function tests, and rapid recovery after stopping cimetidine favour the latter as the cause of her coma rather than hepatic encephalopathy. It is likely that her underlying liver disease predisposed to cimetidine toxicity.

Case 2 800 mg/d

An 80-year-old man with a paraparesis of spinal origin was admitted to hospital with haematemesis, shown by endoscopy to be due to oesophagitis. He had developed moderate anasarca within the previous 6 weeks. The diagnosis of nephrotic syndrome was made by the findings of urine protein of 4 g daily and serum albumin of 16–24 g/litre, and BUN of 32 mmol/litre. Renal biopsy, bone marrow and subsequent liver biopsy showed widespread amyloidosis. Cimetidine 200 mg 4 times daily was given i.v. and thereafter by mouth. On the 5th day, the patient became comatose, reacting only to pain but with no jaundice or asterixis. There was no change in pre-existing renal function tests, and the liver enzyme levels. EEG showed periodic fast low amplitude complexes, compatible with drug-induced effects. Cimetidine was discontinued and mental recovery ensued, although frontal lobe release signs and psychomotor restlessness continued for 24 hr after stopping the drug. The patient was conscious with mild disorientation by the second day after withdrawal of cimetidine, and fully alert by the 4th day.

Comment. The onset of coma without deterioration in the biochemical profile was suggestive of a cause

other than the renal failure. Recovery of consciousness within 2 days of stopping cimetidine pointed to this as the precipitating cause; even in modified dosage of cimetidine the presence of renal failure potentiated the drug's effects on the central nervous system.

Review of literature

Survey of the literature from 1977 to 1981 revealed 47 other patients who were reported as suffering from neuropsychiatric disorders induced by cimetidine (Adler, Sadja and Wilets, 1980; Arslanoglu and Ravry, 1977; Agarwal 1978; Arnesen, 1979; Atkinson, 1980; Barigaloppo, Van-Lint and Marmont, 1978; Balg, 1979; Barbier and Hirsch, 1978; Barnhart and Bowden, 1979; Basavaraju *et al.*, 1980; Cumming and Forster, 1978; Delaunoy, 1979; Edmonds, Ashford and Brenner, 1979; Grimsen 1977; Jefferson, 1979; Johnson and Bailey, 1979; Kinschla, 1980; Kinsch and Webb, 1979; Klotz and Key, 1978; Levine, 1978; McMillen, Ambis and Siegel, 1978; Mendez-Gow, 1977; Noyelnicki, Waller and Poulsson, 1979; Nelson, 1977; Peine and Bloch, 1978; Quap, 1978; Robinson and Mulligan, 1977; Schenag *et al.*, 1978; Vickery, 1978; Wallis, Pearce and Venables, 1980; Weddington *et al.*, 1981; Wood, Hanson and Hibbs, 1978). Up to 1200 mg/d.

Twenty-seven of the patients were male and 19 female. In 4 patients the sex was not reported. The age of 19 patients was 65 years and above, and 27 patients were under the age of 65 years. Conventional doses (up to 1200 mg/24 hr or 20 mg/kg/24 hr) were administered in 45 patients; 5 patients took excess doses. The route of administration was by mouth in 21 and intravenously in 21 patients. Table 1 summarizes the time interval from the onset of treatment until the appearance of the neuropsychiatric side effects. In those cases in which the side effects appeared after increasing the dose of cimetidine the time at which side effects appeared was stated as from the day on which the dose was increased. In 50% neurotoxic effects were prominent within 48 hr. The time until remission occurred was the interval from the day on which the dose was reduced or stopped until relief of symptoms occurred. Almost two-thirds had returned to normal within 2 days. In 5 patients reduction of the dose without stopping the cimetidine brought about relief of the side effects.

The main clinical manifestations were mental confusion (52%), stupor or coma (22%) and neurological abnormalities (16%) such as peripheral neuropathy and pyramidal signs. Psychiatric complications were found in 10% and included depression and paranoid states. *Not good for 24 hr 200 mg/d*

The possible risk factors for developing cimetidine-induced toxicity are analysed in Table 2. Severe

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Discussion

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Table 1. Number of patients in relation to the time of appearance of signs of cimetidine neurotoxicity after the beginning of treatment and the resolution of toxic signs after reducing or stopping the drug

	Appearance of signs	Disappearance of signs
< 2 days	24	12
2-7 days	8	8
> 7 days	10	2
Not reported	8	8

systemic illness without primary disease of the liver or kidney was found in 4 patients. In 6 other patients a gross systemic disease was present in addition to either renal or hepatic failure or both.

Table 2. Predisposing factors to cimetidine neurotoxicity

	No. of patients	%
Impaired renal function	18	20
Impaired renal and hepatic function	8	12
Impaired hepatic function	1	2
Severe underlying disease	4	8
High dose of cimetidine	4	8

Discussion

The literature review indicated that of 50 patients showing neurotoxicity from cimetidine, about 40% were aged 65 years or over. This proportion of elderly patients is much higher than expected among all patients taking cimetidine. Extensive toxicological and pharmacological studies in animals have failed to detect cimetidine in the central nervous system, and neurotoxicity has not been noted (Brinblecombe & Duncan, 1977; Burland *et al.*, 1979; Canadian & Briggs, 1977). Studies in man, however, have shown that the drug may cross the blood brain barrier. Schentag *et al.* (1979) found in 5 patients with severe mental confusion following cimetidine administration that measurable amounts were detectable in the cerebrospinal fluid (CSF). Levels higher than 0.8 mg/ml were considered toxic. In one other report of 2 patients with neurotoxicity, CSF cimetidine levels of 0.83 mg/ml and 0.76 mg/ml were found (Edmonds *et al.*, 1979). These findings suggest that the neurotoxic effect may occur because cimetidine is blocking histamine H_2 receptors in the brain.

There are a few factors which may contribute to the elevation of the CSF levels of cimetidine. High serum concentration is a possibility, which in 5 patients may have been due to treatment with over dosage of cimetidine. However, excessive dosage was

without side effects in a few patients (Gill, 1978; Ringworth & Jarvie, 1979). Other causes for high serum cimetidine concentration are impaired clearance of the drug. Seventeen patients (34%) suffered from impaired hepatic function, renal function or both. The plasma half-life of cimetidine in patients with severe renal failure is doubled (Luk, Luk and Hendrix, 1979). Furthermore cimetidine itself reduces creatinine clearance, and thereby might potentiate its own effect by an increased serum half-life. In addition to this, patients with liver disease showed a CSF/serum cimetidine ratio higher than normal (>0.24) (Schentag *et al.*, 1979), and this suggests the possibility of higher penetrability of the central nervous system to cimetidine.

Nearly 60% of the patients showed signs of toxicity within 2 days of the onset of treatment. Furthermore a few of the patients did not have renal or hepatic failure, or significant underlying disease, and were treated with conventional doses. Such cases indicate a possible individual susceptibility to the effects of cimetidine on the brain. However, elderly patients, including those reported in this paper may present several simultaneous causes for lapse into coma and it is important to appreciate that the presence of renal or hepatic insufficiency may itself potentiate the cerebral effects of cimetidine. Where neurotoxicity is related to one of the above risk factors mentioned, dosage should be decreased and one might expect reversal of mental impairment, as was the case in five patients.

In patients with renal failure, the dosage regimen has been recommended as follows: serum creatinine over 354 $\mu\text{mol/l}$ —150 mg 4 times daily; 177–354 $\mu\text{mol/l}$ —225 mg 4 times daily; less than 177 $\mu\text{mol/l}$ —300 mg 4 times daily (Luk *et al.*, 1979).

This review of 50 patients suggests that cimetidine may be neurotoxic, particularly in old age, in debilitated patients, and in patients with renal or hepatic failure. In all these conditions, patients may be more sensitive to mental changes. However, as cessation of cimetidine resulted in remission in all of the patients and in most of them within 48 hr, use of the drug is not contraindicated in these patients. It is, however, recommended to start treatment with reduced dosage, and to monitor neurological and mental status.

Although trials of a new antihistamine H_2 receptor blocker ranitidine revealed few side effects (Walt *et al.*, 1981), avoidance of neurotoxicity in the presence of renal failure still demands a smaller total daily dose of ranitidine (Borcia *et al.*, 1980; Sharpe and Burland, 1980).

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Cimil recommended at
300 mg 4x/day

Note: Patients w/renal failure cannot take CQ.

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